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Does the addition of ginger decrease migraine pain?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

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Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “does the addition of ginger decrease migraine pain”.

STUDY DESIGN: A systematic review of three peer-reviewed studies published between the years of 2011-2018.

DATA SOURCES: Three double-blinded randomized control trials were chosen from the Cochrane Library and PubMed and selected based on patient oriented outcomes and their relevance to the clinical questions. The study by Martins et al., (*Cephalalgia*. 2018; 39(1):68-76. doi: 10.1177/0333102418776016) compared the addition of ginger vs placebo. The study by Maghbooli et al., (*Phytotherapy Research*. 2014;28(3):412–415. doi: 10.1002/ptr.4996.) compared the addition of ginger vs sumatriptan. The study by Cady et al., (*Headache*. 2011; 51:1078–1086) compared the addition of ginger/feverfew extract vs placebo.

OUTCOME(S) MEASURED: The outcome measured was the reduction of migraine pain 2 hours (2h) post-treatment using patient oriented and reported pain rating using either a four-point scale (0= no pain, 1= mild pain, 2= moderate pain, 3=severe pain) or a visual analogue scale (VAS).

RESULTS: There was an overall decrease in migraine pain 2h post-treatment with the addition of ginger. The study conducted by Martins et al., (*Cephalalgia*. 2018; 39(1):68-76. doi: 10.1177/0333102418776016) showed the addition of ginger significantly reduced migraine pain compared to placebo after 2h post-treatment reported using a four-point pain scale ($p= 0.04$). The study conducted by Maghbooli et al., (*Phytotherapy Research*. 2014;28(3):412–415. doi: 10.1002/ptr.4996.) revealed similar efficacy in reducing migraine pain between the ginger and sumatriptan treatment groups with a reduction of 4.6 units ($p<0.0001$) and 4.7 units ($p<0.0001$) in VAS scores respectively. The study conducted by Cady et al., (*Headache*. 2011; 51:1078–1086) had a significant decrease in migraine pain reported using a four-point scale 2h post-treatment with a decrease from 1.41 to 1.17 ($p=0.01$).

CONCLUSIONS: The evidence presented in this review reveals that the addition of ginger did significantly decrease migraine pain 2h post-treatment. Ginger extract is an affordable supplement that is easily accessible. Further research is warranted to evaluate the effects of ginger on migraine pain as monotherapy and to determine a therapeutic dose.

KEY WORDS: Ginger and migraine

INTRODUCTION

Migraines are a type of primary headache that typically presents as a severe, throbbing, unilateral headache lasting 4-72 hours and may be accompanied by nausea and vomiting. Although not required for diagnosis migraine sufferers may also experience an aura which may present as aphasia, numbness, paresthesia or visual disturbances such as scotomata or photophobia.

Migraines are a common condition that effects 1 in 7 adults in the US and are the most common type of primary headaches that lead emergency department (ED) visits.[1,2] In 2010, they accounted for over 908,000 visits to the ED with an estimated annual cost over $700 million in ED visits.[3] Along with the financial cost, there have been several studies that have shown people suffering from migraines have reported interference with family and social aspects, finances and work leading to a decrease in quality of life.[4,5,6] Migraine patients may be encountered by physician assistants in many medical specialties including primary care for symptomatic and prophylaxis treatment options, neurology to rule out other causes of the neurological symptoms associated with a migraine aura and in the ED for abortive treatments.

Migraines are thought to arise from neurologic dysfunction where vasoactive compounds irritate the trigeminal nerve leading to neurological inflammation. The auras are hypothesized to arise from the cerebral cortex, which manifests as the sensory symptoms that many experience prior to a migraine onset. They typically are also reoccurring and may have triggers including but not limited to missed meals, sleep deprivation, dehydration and stress.

Currently, the basis of treatment is avoidance of known triggers, symptomatic and prophylactic therapy. During an acute attack resting in a dark and quiet room along with simple analgesics such as non-steroidal anti-inflammatories including acetaminophen, ibuprofen and

aspirin, may alleviate pain. In more severe instances stronger prescription medication may be necessary. Ergotamines or triptans may be used for their vasoconstrictive properties, but should be avoided if there is a history of ischemic stroke, peripheral vascular disease, coronary artery disease, uncontrolled hypertension and during pregnancy. Ergotamines and triptans should not be used adjunctively or within 24 hours of each other due to the combined vasoconstrictive effects. Prophylaxis management includes treating comorbidities and choosing medication based on an individual basis. These include beta-blockers, antidepressants, antiepileptic drugs, botox and acupuncture. In the ED morphine, an opioid analgesic, is used as the main abortive therapy.[7] Due to the addictiveness of opioids and the recurrent nature of migraines, it is important to consider other adjunctive treatment options to quickly address migraine pain in acute settings that can be taken regularly.

Ginger extract, known for its anti-inflammatory properties, have been used in past studies to treat migraines. Its active compounds gingeroles and shogaols inhibit cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) leading to a decrease in prostaglandins and leukotrienes respectively.[8] Some studies have also reported that ginger has the potential to reduce platelet aggregation.[9] Given its anti-inflammatory properties, this review evaluates the effect of ginger on migraine pain in three double-blinded randomized control trials.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “does the addition of ginger decreases migraine pain?” The hypothesis is that the addition of ginger will reduce migraine pain when added to migraine treatment regimens in acute settings.

METHODS

Three double-blinded randomized controlled trials (RCT) were reviewed to assess the efficacy of the addition of ginger on migraine pain, as either adjunct therapy or monotherapy. This review focused on the general patient population that suffered from migraines. The efficacy was compared to a placebo group in two of the three studies and sumatriptan in the third study.[10-12] All studies assessed a patient oriented outcome by measuring pain reduction using a patient reported four-point pain scale score or visual analogue score (VAS).[10-12] This systematic review focuses specifically on the effects of ginger in decreasing migraine pain 2 hours (2h) post-treatment.

A specific search criteria was used to select these studies. Keywords used during the search included “ginger” and “migraine”. All three studies were published in peer-review journals, printed in English and selected from the Cochrane Library or PubMed. Inclusion criteria included any RCT within the last ten years and exclusion criteria included anything published before 2008. Statistical analyses in each study used either odds ratio (OR), ANOVA or student t-tests with p-values to determine statistical significance defined as $p < 0.05$.[10-12] The demographics, inclusion and exclusion criteria of each study is presented below in Table 1.[10-12]

OUTCOMES MEASURED

The studies used patient oriented and self-reported results. Martins et al., evaluated change in pain intensity using a four-point scale (0= no pain, 1= mild pain, 2= moderate pain, 3=severe pain) at 0.5h, 1h, 1.5h and 2h post-treatment.[10] Maghbooli et al., evaluated headache severity using a VAS at 0.5h, 1h, 1.5h, 2h, and 24h post-treatment.[11] Cady et al., measured headache severity on a four-point scale (0= no pain, 1= mild pain, 2= moderate pain, 3=severe pain) at 1h

and 2h post-treatment.[12] This article will only focus on migraine severity 2h post-treatment.

Table 1. Demographics of included studies for Ginger and Migraine pain

Study	Type	#Pts	Age	Inclusion Criteria	Exclusion criteria	W/D	Intervention
Martins et al., (2018)[10]	Double blinded RCT	60	Ginger: 33.9 ± 8.3 Control: 35.1± 6.2	18-60 yo, migraine diagnosed ≥1 year, frequency: 1-6 migraines per month	Non-migraine headaches, analgesic use>2x per week, alcohol or drug use, other neurologic diseases, anticoagulant use	0	Addition of 400mg ginger extract divided into two capsules in addition to 100mg IV of ketoprofen for acute migraine attack in the ED. Compared to 100mg IV of ketoprofen and placebo.
Maghoobli et al., (2013)[11]	Double blinded RCT	100	Ginger: 35.1± 6.2 Control: 33.9 ± 8.3	Confirmed migraine diagnosed without aura by neurologist, ≥18 yo, education level: high school diploma or higher, headache frequency between 2-10days per month	History of biliary calculi or peptic ulcer diseases, allergic reaction, hemorrhagic diathesis or using anticoagulants, history of ischemic heart disease, Prinzmetal angina, pregnancy or lactation, headache after head trauma	0	One- 250 mg capsule containing ginger rhizome powder at the onset of headache while keeping up with previous health maintenance therapeutic regimens. Compared to 50 mg sumatriptan.
Cady et al;, (2011)[12]	Double blinded RCT	60	Ginger: 35.1± 6.2 Control: 33.9 ± 8.3	Age: 12-60 yo, met International Headache Society migraine criteria, with or without an aura, history of migraine ≥1 yr, frequency:2-6 per month in the past 3 months and subjects reported ≥ 75% of attacks began with mild headache and they could differentiate between non-migraine and migraine, birth control for women of child-bearing age, stabilized on current medications for at least 90 days	Any medical condition that could confound the results of the study (investigator's opinion), 15 or more headaches per month, utilizing medication for acute migraines 15 or more days per month over the last 3 months, women who were pregnant or breastfeeding, anticoagulant use, known sensitivity to any component of the active study product	1	Addition of sublingual feverfew/ginger drops at the onset of headaches. Participants were asked to wait 2 hours after the sublingual feverfew/ ginger drops before using rescue medication. Compared to placebo.

RESULTS

The study conducted by Martins et al., was a single double blinded, randomized clinical study that included 60 participants, 8 males and 52 females, from the ED of Vera Cruz hospital in Brazil.[10] The participants were randomly allocated into control and treatment groups in a 1:1 ratio using a randomized sequence software generator. [10] In addition to the 100mg IV of ketoprofen received by both groups, the experimental group (n=30) received 400mg of ginger extract as adjunct treatment and the control group (n=30) received an odorless, placebo capsulate with the same color and format as the experiment.[10] There was no noted significant difference between the groups before the start of the trial. [10] It is noted that the exclusion criteria included a history of anticoagulants use due to the anti-platelet effects of ginger.[9,10] The complete list of inclusion and exclusion criteria can be found in Table 1. No participants withdrew or were lost to follow up during this trial. [10]

The outcomes in the study evaluated headache severity using self-reported pain ratings on a four-point scale (0= no pain, 1= mild pain, 2= moderate pain, 3=severe pain) 2h after treatment.[10] The study used crude odds ratio (OR) with a 95% confidence interval (CI) to compare the treatment response of ginger extract vs placebo.[10] P values <0.05 were considered statistically significant. It was observed that the reduction in headache pain from severe/mod to mild/no pain in participants that received ginger extract at 2h post-treatment as compared to the placebo was significant ($p=0.04$) as shown in Table 2.[10] There was a higher proportion of patients that reported being pain free 2h post-treatment with ginger extract vs the placebo (56.7 vs 33.3, $p=0.03$).[10] The OR of 7.25 with a CI of 0.81-64.45 ($p=0.07$) after 2h can be found in Table 3.[10] The OR of 7.25 suggests that improvement in headache severity is 7.25 times higher in patients that received ginger as part of their treatment as compared to the placebo indicating a

strong association. However, the p-value of 0.07 makes this association not statistically significant.

Table 2. Reduction in migraine intensity reported by four-point scale[10]

Time	2h
Placebo	0.97 ±0.07
Ginger	0.81 ±0.04
p-value	0.04

Table 3. Response to treatment of migraine pain with ginger extract vs placebo using OR[10]

Time	2h
OR	7.25
CI 95%	0.81-64.45
p-value	0.07

The study conducted by Maghbooli et al., was a single double blinded, randomized clinical study with 100 participants, 71 females and 29 males, enrolled from the Neurology Clinic of Zanjan Vali-e-Asr Hospital in Iran.[11] The participants were randomly assigned to two coequal groups.[11] Both groups received a box containing five capsules of either 50mg sumatriptan for the control group (n=50) or 250mg powder ginger rhizome for the experimental group (n=50).[11] Participants were kept on their maintenance therapy and were advised to take one capsule with the onset of their migraine for one-month.[11] There was no noted significant difference between the groups before the start of the trial.[11] It is noted that the exclusion criteria included a history of bleeding diathesis or use of anticoagulants due to the anticoagulant effects of ginger and ischemic heart disease or Prinzmetal's angina due to the vasoconstrictive effects of sumatriptan.[11] The complete list of inclusion and exclusion criteria can be found in Table 1. No participants withdrew or were lost to follow up during this trial.[11]

The outcomes in the study evaluated the headache severity using self-reported visual analogue scale (VAS) after 2h of treatment administration.[11] Results were analyzed using student t-tests and two-tailed p-values to assess treatment response, with $p<0.05$ considered significant.[11]

Similar efficacy at 2h post-treatment was observed in sumatriptan and ginger groups, revealing a unit reduction of 4.7 ($p<0.0001$) and 4.6 ($p<0.0001$) on the VAS respectively.[11] The continuous data presented in the study was converted into dichotomous data by defining "improvement" as patients with a baseline "moderate or severe" headaches that measured "free of headaches" after 2h, and "no improvement" as patients that measured "mild headaches" after 2h. This was done for both the ginger and sumatriptan groups and can be found in Table 4. The NNH indicates that for every 34 people that are treated with ginger, one person will have a negative or adverse effect, making this a small treatment effect. The relative benefit increase (RBI) of 5.27% further supports this intervention to have a small treatment effect.

Table 4. Efficacy of Ginger in Reducing Migraine Pain

Study	EER	CER	RBI	ABI	NNT	NNH
Maghbooli et al., [11]	60.7%	63.9%	5.27%	-0.032	----	34
Cady et al., [12]	57.0%	37.9%	50.4%	0.191	6	----

EER: experimental event rate; CER: control event rate; RBI: relative benefit increase; ABI: absolute benefit increase; NNT: number needed to treat; NNH: number needed to harm

The study conducted by Cady et al., was a double blinded, randomized clinical study with 60 participants, 14 males and 46 females, conducted at three sites in the USA over a one-month period.[12] It is noted that one patient withdrew because of pregnancy.[12] The participants were randomly assigned using an online generator to the experimental group (n=45) and placebo group (n=15) at a ratio of 3:1.[12] Both groups were encouraged to administer two units of their sublingual drops five minutes apart at the onset of mild migraine pain.[12] Another administration of two units in the same manner was acceptable if the headache pain persisted for one hour.[12] Additional rescue medication, once approved by the case investigator, was allowed if pain persisted for two hours after the first treatment.[12] This study was generalized to children >12 years old, men and non-pregnant women that suffered from migraines.[12] It is noted that the

exclusion criteria included a history of anticoagulants use due to the anticoagulant effects of ginger.[12] The full list of inclusion and exclusion criteria can be found in Table 1.

The outcomes in the study evaluated headache severity using self-reported ratings on a four-point scale (0= no pain, 1= mild pain, 2= moderate pain, 3=severe pain) after 2h of treatment administration.[12] The data was analyzed using a 2-way analysis of variance (ANOVA) and p-values, with values $p<0.05$ considered statistically significant.[12] It is noted that there was "modest randomized imbalance and significant difference between the two groups" at the time of treatment.[12] The initial headache severity for the active and placebo group was 1.41 and 1.67 respectively ($p=0.01$).[12] At 2h post-treatment there was a significant decrease in headache severity in the experiment group (1.41 to 1.17, $p=0.01$) compared to the placebo (1.67 to 1.71, $p=0.81$). [12] Thirty-two percent of subjects reported being pain free 2h post-treatment when taking sublingual feverfew/ginger as opposed to 16% reported being pain free when taking the placebo ($p=0.02$).[12]

The continuous data presented in the study was converted into dichotomous data by defining "improvement" as participants who reported having "no pain or mild pain" after 2h, and "no improvement" as participants that measured "moderate or severe" after 2h. This was done for both the experiment and placebo group and can be found in Table 4. The NNT of 6 indicated that for every six people that are treated with feverfew/ginger sublingual drops there will be one person that will have beneficial migraine pain reduction, making this a small treatment effect. The RBI of 50.4% further suggests this intervention is a small treatment effect.

Safety and tolerability

Overall, the addition of ginger was well tolerated in all three studies. In the study by Martins et al., three participant reported dyspepsia after 0.5h post-treatment and only one

participant still had symptoms after 2h post-treatment.[10] The study by Maghbooli et al., also reported dyspepsia. [11] The study by Cady et al., reported mild adverse effects with the ginger/feverfew treatment that were similar to the placebo except for oral numbness. These adverse effects included but are not limited to nausea, oral numbness, vomiting and stomach cramps. [12]

DISCUSSION

The three double-blinded RCTs found that the addition of ginger does decrease migraine pain, however, the treatment effect is not large. In the study by Martins et al., there was a significant decrease in migraine pain after 2h post-treatment when comparing the headache severity between the two groups and more patients reported being pain-free when receiving ginger after 2h.[10] Although the study had an OR of 7.25, this was statistically insignificant ($p=0.07$) as discussed above. In the study by Maghbooli et al., there was no significant difference in the efficacy of ginger when compared to sumatriptan in decreasing migraine pain.[11] The NNH was calculated to be 34 making this treatment effect small. However, this finding should be taken into consideration in patients with comorbidities that are contraindications to triptans (i.e. hypertension or coronary artery disease) making the addition of ginger a possible treatment option. In the final article conducted by Cady et al., there was a significant decrease in migraine pain with the addition of ginger, however, the NNT of 6 makes this a small treatment effect. It is also noted that the ABI of 0.191 indicates that people that add ginger to their treatment regimen are only 19% more likely to have a decrease in migraine symptoms which further suggests this is a small treatment effect.[12]

Limitations

Other factors to take into consideration includes the quality, accessibility and dosage amount needed for adjunctive treatment. Ginger extract can be found in many drug and food stores as a supplement, but it is not approved or regulated by the FDA.[13] Although most insurance drug coverage plans do not cover vitamins and supplements, ginger can be purchased out of pocket for $9-$16 for 120 capsules of 550mg.[14] Unfortunately, there are not enough studies that have been conducted to determine the therapeutic amount needed to alleviate migraine pain which makes dosage recommendations difficult.

In the article by Martins et al., one of the limitations was that the treatment plan was to use the ginger extract or placebo pill adjunctively with ketoprofen, an analgesic which in itself contributes to the decrease in migraine pain severity.[10] The article by Maghbooli et al., had a similar limitation, in which their participants were allowed to continue their previous maintenance therapeutic agents.[11] In the article by Cady et al., they used a randomization ratio of 3:1 feverfew/ginger combination to placebo, which makes the study biased towards the experiment group.[12] It is also noted that although the placebo did not include an active analgesic, feverfew itself has been shown to have anti-inflammatory properties which may have contributed to the decrease in headache severity reported by participants.[15]

CONCLUSION

The three articles analyzed in this systematic review suggests that the addition of ginger does decrease migraine pain, which supports the hypothesis of this systematic review. However, the treatment effects are small as discussed above. When determining whether or not to consider ginger as adjuvant treatment for migraine pain it is important to consider all costs and benefits of treatment and recommendations should be individualized.

A limitation to this systematic review is that the amount of ginger used in treatment groups varied between the studies, which could lead to inconsistent treatment effects since there is currently no standardized recommended treatment dose. There is a limited number of studies that have been carried out to evaluate the effects of ginger on migraine pain, which also warrants future studies. More studies are needed using a larger participant population, studies to evaluate ginger's effects as monotherapy and studies comparing ginger to a placebo rather than another medication intervention to fully understand its effects. The anti-inflammatory effects of ginger are promising and should remain an area of continuous research for the treatment of migraine pain.

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